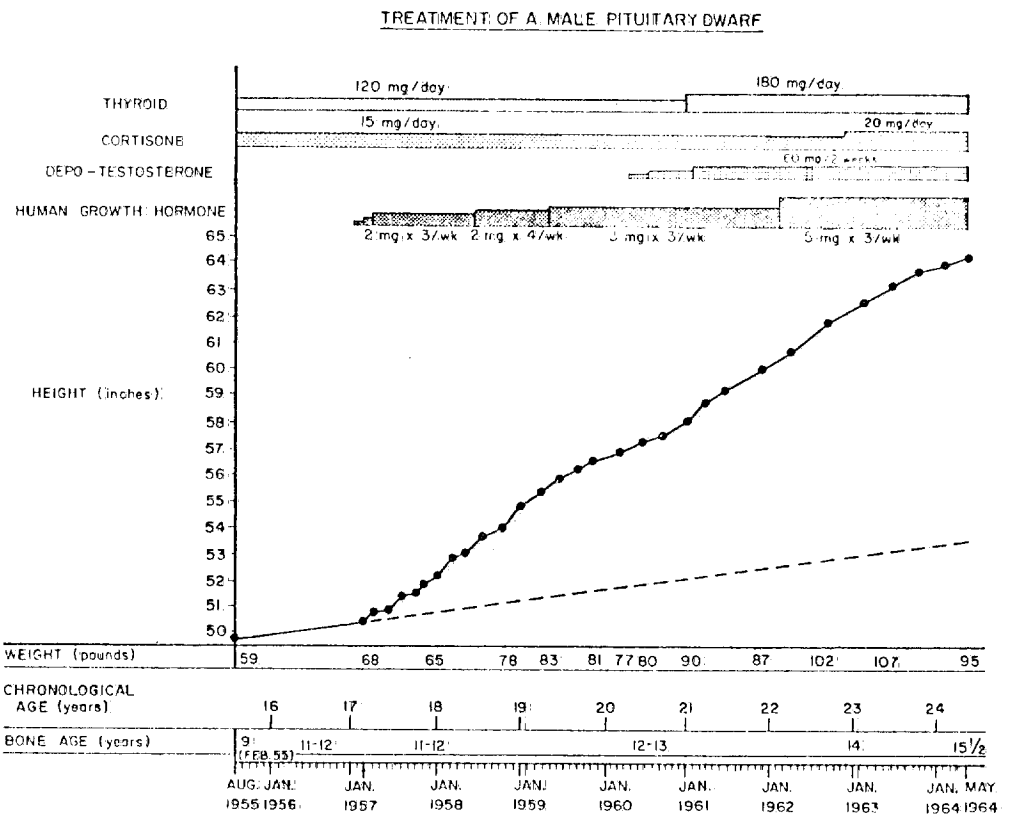

Figure 66-1. *Treatment of a patient with pituitary dwarfism with human growth hormone during replacement therapy with thyroid, cortisone, and testosterone.* (Modified from Raben, 1962b. Courtesy of the *New England Journal of Medicine.*)

To select those cases of short stature that are caused by deficient growth hormone, it is necessary to measure the growth hormone in the serum and to determine whether there is an appropriate response to a provocative stimulus. A requirement for therapy with growth hormone is based on the clinical findings and failure to respond to two or more provocative stimuli for secretion of the hormone. Once initiated, therapy should be evaluated for 8 to 12 months for the expected acceleration of growth. If therapy is successful, it should ideally be continued throughout childhood, and sex hormones, if needed, should be withheld until the possibilities of the response to growth hormone have been fully realized or until deemed necessary.

Undesirable side effects and complications are notably lacking; pain and swelling at sites of injection, allergic reactions, and chronic ill effects do not occur even when serum antibodies can be shown.

Human growth hormone is currently available in the United States only for treatment programs that include research efforts. It is obtained from the National Pituitary Agency of the National Institutes of Health, Bethesda, Maryland, upon approval of its Medical Advisory Committee. Hormone is supplied for a specific patient, and with yearly reapplication the supply is usually committed until the patient attains a height of 5 ft. It is estimated that the available supply of hormone is sufficient for treatment of only 10% of the hypopituitary children in the United States. All pathologists should cooperate by sending human pituitaries obtained at post-mortem examination to the National Pituitary Agency.

PROLACTIN

Despite a wealth of information about the nature and role of prolactin in a wide variety of species, unequivocal evidence for the existence of the hormone in man was obtained relatively recently (*see* Frantz *et al.*, 1972). It is now appreciated, however, that prolactin plays an important role in normal human function and in certain pathophysiological states.

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1974; Boston Collaborative Drug Surveillance Program, 1974; Heinonen *et al.*, 1974).

Ovary. The effects of prolactin on the ovary are species dependent. While the hormone has in the past also been referred to as *luteotropin*, this description was based on observations on rats and mice. In these species prolactin can prolong the life of the functioning corpus luteum, but it probably does not fulfill the role of a true luteotropic hormone. Notably, prolactin will not stimulate progesterone biosynthesis by corpora lutea from a variety of species, including rats (*see* Dorfman, 1972). It may, however, function to promote the luteal synthesis of cholesterol, the steroidal precursor. In contrast, luteinizing hormone is uniformly effective in stimulating progesterone synthesis. Surprisingly, recent evidence suggests that the sharp rise in prolactin secretion seen during proestrus in the rat may be responsible for luteolysis of corpora lutea formed during the previous cycle (Meites *et al.*, 1972).

Significant effects of prolactin on the human ovary are not known, and large variations of plasma prolactin concentrations are not apparent at different stages of the menstrual cycle.

Prolactin Secretion. Refined assay technics not only have been instrumental in the identification and purification of human prolactin but also have allowed exploration of physiological, pathological, and pharmacological influences on prolactin secretion (*see* Frantz *et al.*, 1972; Friesen, 1973).

The normal human plasma concentration of prolactin approximates 5 to 10 ng/ml and is essentially the same in males and females. Prolactin concentrations rise markedly during pregnancy, reaching a maximum at term. In nursing mothers prolactin secretion is critically controlled by the sucking stimulus or breast manipulation. Prolactin concentration can rise 10- to 100-fold within 30 minutes of stimulation. Other stimuli for prolactin secretion include psychic and physical stress, insulin-induced hypoglycemia, and high doses of estrogens. Interestingly, hypertonicity results in large elevations of plasma prolactin (Buckman and Peake, 1973). Future work should reveal whether any physiological significance is attached to this phenomenon or if it represents an undiscarded heritage of the *water-drive factor*.

Secretion of prolactin by the pituitary is under predominantly negative control by the hypothalamus. Thus, a prolactin release inhibiting hormone (PRIH) is secreted tonically by the hypothalamus and is carried by the hypothalamicoadenohypophyseal portal system to the adenohypophysis, where it inhibits prolactin secretion. There is considerable evidence that the release of PRIH is under adrenergic (dopaminergic) control, or that PRIH might even be dopamine (MacLeod and Lehmeyer, 1974). Thus, the administration of levodopa *in vivo* inhibits prolactin secretion, and dopamine is a highly effective inhibitor when instilled into the third ventricle or when applied to the isolated pituitary *in vitro*. Predictably, the phenothiazine and butyrophenone antipsychotics (*e.g.*, chlorpromazine, haloperidol), which are dopamine antagonists, enhance prolactin secretion, as can reserpine and α-methyldopa. The antipsychotic agents can cause significant galactorrhea associated with elevated plasma prolactin concentrations.

Functional disorders of the hypothalamus (Chiari-Frommel syndrome) and destructive or infiltrative disorders of the hypothalamus or pituitary stalk can also cause prolactin secretion and galactorrhea if there is interference with the tonic inhibitory hypothalamic influence. Pituitary oversecretion of prolactin, often due to functional tumors (Forbes-Albright syndrome), is also known. However, in none of these conditions is there strict correlation between plasma prolactin concentration and the presence or severity of galactorrhea.

Suppression of galactorrhea by administration of levodopa has been attempted with variable success (Turkington, 1972). Some patients who respond initially become refractory to the drug. More promising clinical results have been achieved with ergot derivatives (Floss *et al.*, 1973). Inhibition of lactation in women suffering from ergotism was observed centuries ago. This phenomenon has recently gained scientific credence with the discovery that ergot derivatives profoundly inhibit prolactin secretion *in vivo* and in isolated pituitary preparations *in vitro*. Since the inhibitory effect *in vitro* is antagonized by haloperidol, it is possible to hypothesize that ergot alkaloids activate the dopaminergic receptors that inhibit prolactin release. The experimental compound that has shown significant clinical promise is 2-bromo-α-ergokryptine. An additional finding of potential significance is that this compound can markedly suppress the growth of prolactin-secreting pituitary tumors (Quadri *et al.*, 1972).

Assays. The classical procedure for bioassay of prolactin is based on the original work of Riddle and associates (1933), namely, the increase in weight of the crop sacs of doves and pigeons. Other methods are based on the induction of secretory changes in the suitably prepared mammary glands of guinea pigs and rabbits. As mentioned above, radioimmunoassays have proven invaluable. A radioreceptor assay that utilizes a membrane receptor preparation isolated from rabbit mammary glands should also be useful to assess biological activity (Shiu *et al.*, 1973).

Human Placental Lactogen. Preparations from the human placenta contain growth-promoting and lactogenic activity (*see* Fukushima, 1961); Josimovich and MacLaren (1962) showed that such extracts cross-reacted with antisera to human growth hormone. Purified preparations caused a local response in the crop sac of the pigeon and maintained the function of the corpora lutea of rats but caused little

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Prolactin is widely distributed in the pituitaries of vertebrates; it has been found wherever sought in the pituitaries of mammals, birds, reptiles, and amphibia, and has been detected in a few species of fish. Among the amphibia, it has a clear-cut and very striking action in the newt *Triturus*, an action almost as remarkable as the metamorphic one of thyroid hormone on tadpoles. It transforms the terrestrial eft—a small, pink quadruped found under rocks in the woods—into a larger, dark-green, fish-shaped creature with a broad tail designed for swimming. The animal then takes to the water, its normal breeding habitat, which accounts for the term *water-drive factor* coined before the active principle was equated with prolactin (Bern and Nicoll, 1968).

The term *prolactin* was coined for the hormone responsible for the secretion of milk by the crop glands of the pigeon (Riddle *et al.*, 1933). In this bird there is a bilateral outpouching of the esophagus and, prompted by the psychological concomitants of brooding, a glandular structure grows within each pouch so that by the time of hatching a thick secretion, the crop milk, becomes available to each parent for regurgitating down the throats of the young. The response of the bird is a sensitive one; it is sufficient for one partner to see his mate sitting on the eggs for his pituitary to secrete prolactin and provoke the growth of the crop glands. In so naming the hormone, the tenuous analogy between the mammary gland and the crop sac was correctly drawn because it later was clear that prolactin is also of importance in initiating secretion from the breast.

Chemistry. The difficulty in isolating human prolactin is attributable to the facts that growth hormone is very similar in structure, possesses significant lactogenic activity in conventional bioassays for the hormone, and is present in human pituitaries in quantities far in excess of prolactin. However, refined bioassay technics permitted verification of the existence of human prolactin (Frantz and Kleinberg, 1970), and the technic of affinity chromatography permitted purification of a primate prolactin and subsequent development of a specific radioimmunoassay (Guyda and Friesen, 1971; Hwang *et al.*, 1971). Progress in the purification, chemistry, and physiology of human prolactin has been rapid since these advances.

Amino acid sequence determination of the amino-terminal region of the hormone (residues 1–50) has revealed approximately 25% identity and 50% homology with human growth hormone. There is high conservation of structure between human and ovine prolactin (80% identity), at least in this region, and the structure of the human hormone undoubtedly resembles closely that of sheep (Niall *et al.*, 1973).

Ovine prolactin has been characterized extensively, since the pituitaries of sheep are readily available and constitute a very rich source (Li *et al.*, 1970). The general structural features are very similar to those of the growth hormones (Table 66-1); the proposed evolutionary relationship of these molecules has been discussed above. As with the growth hormones, "isohormones" with presumed minor structural differences can be detected by electrophoresis.

Physiological Actions. *Breast.* The mammary gland is a site of immensely complex interactions among a number of hormones, with the majority of endocrine organs participating vigorously in the initiation and maintenance of lactation. The hormones of the adrenal cortex, thyroid, and ovaries are all necessary, and their presence is dependent on the trophic hormones of the adenohypophysis. Insulin and perhaps growth hormone exert important anabolic influences. The vital participation of prolactin completes the contribution of the anterior pituitary, with all of its major secretions at work. The role of oxytocin is considered in Chapter 42.

The actions of prolactin on the mammary gland have been studied particularly in explanted rodent tissue. However, investigations of normal and aberrant prolactin secretion seem to assure the existence of a comparable function in the human female. In systems *in vitro*, prolactin in the proper hormonal milieu can be shown to promote proliferation and subsequent differentiation of mammary ductal and alveolar epithelium. There is a rapid increase in RNA synthesis and induction of the synthesis of milk proteins and of enzymes necessary for lactose synthesis (Topper, 1970; Turkington *et al.*, 1973). At the subcellular level, activation of the development of rough endoplasmic reticulum, Golgi apparatus, and secretory granules is prominent.

These "mammotrophic" actions of prolactin suggest a possible role of prolactin in mammary tumorigenesis. Prolonged prolactin administration, the grafting of extra pituitaries, or experimental lesions in the median eminence that cause increased prolactin secretion all result in a high percentage of mammary tumors in susceptible rats and mice. Furthermore, estrogen will not produce tumors in the absence of the pituitary; however, in rats treated with carcinogens, prolactin promotes tumorigenesis in the absence of estrogens or progestins. Furthermore, drugs that enhance prolactin secretion (*e.g.*, reserpine, haloperidol—*see* below) facilitate experimental tumor growth, while those that inhibit secretion (*e.g.*, ergot derivatives) impede growth and reduce the incidence of spontaneous tumors in rodent models (*see* Meites *et al.*, 1972; McMahon *et al.*, 1973). Extrapolation between highly susceptible strains of rodents and man is obviously of questionable value, but these observations may provide additional explanations for the effectiveness of hormonal therapy of breast tumors. They may also relate to reports of the increased incidence of breast cancer among women who have been treated with reserpine for hypertension (*see* Armstrong *et al.*,

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growth in hypophysectomized animals; the active principle was named *placental lactogen*. Friesen (1965, 1966) purified the protein to homogeneity and demonstrated that it was strikingly lactogenic in pseudopregnant rabbits.

The chemical similarity of the substance to human growth hormone was shown by Sherwood (1967), and the complete amino acid sequence has been elucidated by Niall and associates (1971) and Li and coworkers (1973). The resemblance to growth hormone was amply confirmed by these studies, since both hormones contain 191 amino acids that differ in only 32 positions. The greater similarity of amino acid sequence in human placental lactogen and human growth hormone than in human and bovine growth hormones suggests a later evolutionary appearance of the placental lactogen. Its significance is, however, largely unknown. Because of its resemblance to growth hormone, the unwieldy name *chorionic somatomammotropin* is also in use.

GONADOTROPIC HORMONES

The pituitary gland plays an important part in the regulation of gonadal function throughout the vertebrate phylum, but the fullest understanding of the mechanisms involved has been achieved among the mammals. In this class there are striking species differences, with remarkable specialization in some as well as a certain uniformity among others, permitting the formulation of general principles. The adenohypophysis is physiologically and anatomically so situated that it can mediate neural messages that arise from the environment as well as intercept humoral signals from within. It can regulate such diverse phenomena as the annual growth and regression of the gonads of monestrous mammals in response to the changing length of daylight, the release of ova in the rabbit 10 hours after mating, and the reinitiation of follicular growth when a corpus luteum fails for lack of successful impregnation.

For over 40 years it has been known that two gonadotropins are involved, and it seems a general rule among mammals that follicular growth and development on the one hand and ovulation and the formation of a corpus luteum on the other are separately controlled. These same substances stimulate, respectively, the germinal elements of the testis and the androgen-secreting Leydig cells of the interstitial tissue. In the regulation of the function of the corpus luteum, several adaptations have arisen. In some species luteinizing hormone serves as the luteotropin, in others prolactin plays such a role, while in several species the uterus is somehow involved. During pregnancy the pituitary seems essential in some animals, while in most it is dispensable; luteal function may be autonomous, as in the herbivora, or regulated in part by a placental luteotropin, as in man.

Until very recently the functions of the gonadotropins in man were largely inferred from information derived from other mammals. Direct observations on human beings of the effects of gonadal hormones and their analogs and human gonadotropins have given better understanding and have opened new therapeutic approaches to the disturbances of human reproductive function.

Chemistry. The four gonadotropins considered here (two of pituitary and two of placental origin) are follicle-stimulating hormone (FSH), luteinizing hormone (LH), chorionic gonadotropin (CG), and the gonadotropin of pregnant mares' serum. The gonadotropins, with thyrotropin (TSH), constitute the glycoprotein group of hormones, and their similarities and general chemical features have been mentioned above (*see* Table 66-1).

Follicle-stimulating hormone (*FSH*) is the least well characterized of the pituitary hormones and the only one for which detailed information on amino acid sequence is not known. However, it is known that the human hormone consists of nonidentical, noncovalently linked subunits (Saxena and Rathnam, 1971). While the α subunit of FSH is significantly different from that of LH or TSH (Papkoff, 1972), there is evidence that the FSH α subunit can combine with the β subunit of chorionic gonadotropin with restoration of chorionic gonadotropin activity (Reichert, 1972).

Luteinizing hormone (*LH*), also called *interstitial cell-stimulating hormone*, more closely resembles TSH in its physical properties and chemical constitution than it does FSH. Ovine LH-α is identical to bovine TSH-α, and the β subunits show considerable homology. Considerable progress has been made with human LH, and the amino acid sequences of both α and β subunits have been reported (Sairam *et al.*, 1972; Shome and Parlow, 1973). Approximately 70% of the amino acid residues of both subunits are identical to the corresponding portions of the ovine hormone (Liu *et al.*, 1972a, 1972b). Many differences are explicable by a single DNA base change. Human LH-β is even more similar to a major portion of the β subunit of human chorionic gonadotropin, although the latter has a 30 amino acid carboxyl-terminal segment that is not present in human LH-β.

Human chorionic gonadotropin (*HCG*) is prepared

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